

### REMARKS

Claims 1-5, 8, 9, and 35-44 are presently pending in the application. Claims 1, 5, and 37 has been amended for clarity. Support for the use of the term "level" rather than "magnitude" is supported throughout the specification (see, for example, page 5, lines 3-14). New claims 43 and 44 are supported by, for example, original claim 7. No new matter has been added.

At the outset, Applicants thank Examiner Tung for her time and helpful remarks made to Applicants' representatives, Lee Crews and Margo Furman, during the telephone interview held on May 18, 2004. The substance of the interview is discussed below.

#### Non-finality of the Action

In the Office action mailed November 19, 2003, both box 2a (which states "This action is FINAL") and box 2b (which states "This action is non-final) were checked. In a telephone conference of May 7, 2004, with Margo Furman, Examiner Tung stated that the action was non-final. Should the Office find, for some reason, that a Notice of Appeal is required to maintain the present application, Applicants have filed a Notice of Appeal herewith with the required fee. Applicants request that the Examiner clarify the non-finality of the Office action mailed November 19, 2003 in writing for the record.

#### Rejections under 35 U.S.C. § 103

Claims 1-5, 8, 9, and 35-42 were rejected under 35 U.S.C. § 103 as unpatentable over Strom *et al.* (U.S. Pat. No. 6,187,543; "Strom") in view of Soares *et al.* (*Nature Medicine*, 1998, vol. 4(9):1073-1077; "Soares"). The Examiner states (Office action at page 2):

Strom *et al.* disclose a method of evaluating transplant rejection in a host comprising determining a heightened magnitude of gene expression of immune activation marker gene in a tissue biopsy or peripheral blood mononuclear cell sample.

However, the Examiner also recognized that Strom says nothing about the two genes -- HO1 and A20-- specifically recited in Applicants' claim 1. The Examiner states (Office action at page 2):

Strom et al. do not disclose determining the magnitude of gene expression of gene, heme oxygenase 1 (HO1) or A20 for monitoring the status of a transplanted organ in a host.

Turning to the secondary reference, Soares, the Examiner states (Office action at page 2):

Soares et al. disclose that the expression of the heme oxygenase-1 (HO-1) is functionally associated with xenograft survival and that rapid expression of HO-1 in cardiac xenografts can be essential to ensure long-term xenograft survival.

The Examiner's conclusion is (Office action at page 3):

One of ordinary skill in the art at the time of the instant invention would have been motivated to apply the method of Strom et al. to evaluate acute transplant rejection in a host by determining the magnitude of the expression of the gene, HO-1 or A20...It would have been prima facie obvious to monitor the status of a transplanted organ in a host by determining the magnitude of the gene expression of the gene, HO-1 or A20.

This rejection is respectfully traversed. As was discussed in the interview of May 18, 2004, and as is reviewed below, neither Strom, Soares, nor the combination of these references satisfy the basic requirements of a *prima facie* case of obviousness.

#### The present claims

Much of the discussion during the interview of May 18, 2004, focused on the way in which the method now claimed differs from any method disclosed in Strom or Soares. As noted then, the present claims cover a method for monitoring the status of a transplanted organ in a host, such as a human patient. Applicants have discovered that upregulation of particular genes indicates increased likelihood of graft rejection, and the steps of the claimed method conclude by determining whether the gene(s) are upregulated. In the interview, the Examiner asked that Applicants clarify the meaning of "upregulation" as used in their claims. Applicants direct the

Examiner to the phrase at page 3, line 30, of the specification, where Applicants refer to “upregulation of gene expression” as “increased or heightened gene expression.”

This passage is consistent with the use of the term “upregulation” as it is used in the art to refer to increased gene expression. As described in the specification, methods for determining levels of gene expression include methods wherein mRNA (the “messenger” produced when genes are transcribed) levels are measured. See, for example, the section of the specification entitled “Detecting Gene Expression”, beginning at page 24, line 18. Thus, the present claims cover methods for detecting increased expression of particular genes. It is this increased expression that indicates that the host is likely to experience transplant rejection.

To clarify claim 1, Applicants have added a “determining” step (step (d)) and a clause at the end of the claim that relates back to the preamble: it is by determining whether a gene was upregulated that one has an indication that the host is likely to experience transplant rejection.

#### The references cited (Strom and Soares)

The Examiner relies on Strom as disclosing methods of evaluating transplant rejection by determining “a heightened magnitude of gene expression in [sic] immune activation genes [sic]” (Office action at page 2). As the Examiner noted, Strom does not disclose methods wherein expression of HO-1 or A20, or genes that are coordinately regulated with these genes, is examined. Strom is silent with respect to these genes. Accordingly, Strom does not teach or suggest all of the limitations of the methods now claimed (a requirement for *prima facie* obviousness).

We turn then to the secondary reference, Soares. The Examiner relies on Soares as disclosing that expression of HO-1 correlates with graft survival. As discussed during the telephone interview of May 18, 2004, Soares fails to meet the requirements for obviousness because Soares teaches away from the claimed invention. Applicants have shown that increased expression of HO-1 correlates with increased likelihood of graft rejection. Soares reports the opposite finding. Soares observed that HO-1 expression is associated with increased graft survival. See, for example, the last sentence of the abstract of Soares which states “we show here that the expression of the HO-1 gene is functionally associated with xenograft survival, and

that rapid expression of HO-1 in cardiac xenografts can be essential to ensure long-term xenograft survival.” Thus, even if one were motivated to combine Strom with Soares, one would still not arrive at the method now claimed. Combining Strom with Soares, if anything, would lead to a method in which increased expression of HO-1 indicates graft survival. To the contrary, in Applicants method, increased expression of HO-1 is an indication of graft rejection.

In view of the foregoing, Applicants ask that the rejection of the claims under 35 U.S.C. § 103 be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-5, 8, 9, and 35-42 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Examiner stated that the claims are indefinite because “the preamble states that the method is for monitoring the status of a transplanted organ in a host, but there is no monitoring step in the method step. Clarification is required.”

Applicants have amended claim 1 to make it clear that by performing the steps of the claimed method, one is monitoring the status of the organ. The steps, which now include step (d), produce a result that indicates whether the host is likely to experience transplant rejection. By determining that likelihood, one is monitoring the status of the transplanted organ (as set out in the preamble).

Concluding Remarks

In view of the foregoing amendment and remarks, Applicants contend that the present claims are now in condition for allowance. Should the Examiner require clarification of any of the statements made above, the favor of a telephone call is respectfully requested.

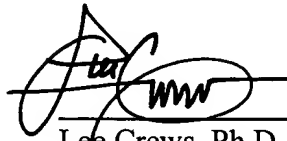
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Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: May 19, 2004

A handwritten signature in black ink, appearing to read "Lee Crews", is written over a horizontal line.

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